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EXAMINER	
RAWLINGS,S	
ART UNIT	**PAPER NUMBER**
1642	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/606,042	AIN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *1-19* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Claims 1-19 are pending in the application. Claims 17-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

2. Claims 1-16 are currently under prosecution.

Election/Restrictions

3. Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group 1. Claims 1-16, drawn to a method for expressing a tumor specific therapeutic response element in a cancerous cell, classified in class 435, subclass 325.

Group 2. Claims 17-19, drawn to a method for treating a tumor, classified in class 424, subclass 9.2.

4. The inventions are distinct, each from the other because of the following reasons:

The inventions in Groups 1 and 2 are disclosed as materially different methods that differ at least in objectives, method steps, reagents and/or doses and/or schedules used, response variables, assays for end products and/or results, and criteria for success and therefore, the claimed methods are distinct.

5. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

6. During a telephone conversation with Joseph Hyosuk Kim on March 29, 2001 a provisional election was made with traverse to prosecute the invention of Group 1, claims 1-16. Affirmation of this election must be made by applicant in replying to this

Office action. Claims 17-19 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

8. On page 15, lines 31-34, the specification appear to be contradictory, indicating that the cell line KAK-10 is derived from both a papillary carcinoma and a benign follicular neoplasm. Appropriate correction is suggested.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing the re-expression of the previously silenced endogenous gene encoding human sodium/iodide symporter in the human thyroid typical papillary carcinoma cell lines, including KAK-5, KAK-10 and NPA'87, and in the human benign follicular adenoma cell line KAK-1, said method comprising a step of administering 5-azacytidine, sodium butyrate, or phenylacetate to the cell line does not reasonably provide enablement for a method for inducing the re-expression of any previously silenced endogenous or exogenous gene encoding a therapeutic response element in any cancerous cell, wherein any demethylating agent is administered to the cell. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a method for inducing the re-expression of any gene in any cancerous cell that was previously silenced by methylation, wherein said method comprises a step of administering any deblocking agent that re-activates expression of the gene, wherein said gene is endogenous or exogenous to the cell or wherein the cell to be treated is dedifferentiated or wherein the agent activates a transcription factor that facilitates activation of the gene.

The specification discloses that the method of re-expressing the previously silenced gene encoding the sodium/iodide symporter is useful since the reactivation of the gene can increase the efficacy of anti-tumor radiotherapy in patients diagnosed with dedifferentiated thyroid cancer (see, for example, page 4, lines 19-24). The specification teaches that treatment of the human thyroid typical papillary carcinoma cell lines, namely KAK-5, KAK-10 and NPA'87, and the human benign follicular adenoma cell line KAK-1 with either 5-azacytidine, sodium butyrate, or phenylacetate restores the expression of the previously silenced encoding the human sodium/iodide symporter (page 22, Table 2). Furthermore, the specification discloses in Table 2 that either sodium butyrate or phenylacetate, but not both agents, is capable of restoring the expression of the gene in the papillary carcinoma cell lines, but neither agent is capable of restoring the expression of the gene in the follicular adenoma cell line. Only 5-azacytidine is capable of restoring the expression of the gene in each of the four cell lines (Table 2); however, neither 5-azacytidine, sodium butyrate, nor phenylacetate can restore the expression of the gene in every dedifferentiated thyroid cancer cell line tested (page 15, line 29 – page 16, line 5). The specification teaches that though iodide is not taken up by anaplastic thyroid carcinoma cells, the gene encoding the sodium/iodide symporter is expressed (page 7, lines 29-35). Moreover, the specification teaches that most follicular, typical papillary, and anaplastic dedifferentiated thyroid carcinomas express the gene encoding the sodium/iodide symporter (page 14, lines 28-31). The specification also discloses that there are six cases in which there is a lack of concordance between the expression or lack thereof of

the gene encoding the sodium/iodide symporter and the uptake of iodide by a dedifferentiated thyroid carcinoma (page 14, line 32 – page 15, line 3). The specification teaches that there appears to be a correlation between the level of expression of the gene encoding the sodium/iodide symporter and the extent to which the gene is methylated in the tall-cell variant papillary carcinoma (page 14, lines 26-28). However, the lack of expression of the gene encoding the sodium/iodide symporter in tall-cell variant papillary carcinoma tumors cannot be assuredly explained by the methylation status of the gene (page 8, lines 24-26). Finally, the specification discloses that there are other mechanisms, apart from hypermethylation of the CpG islands contained within the regulatory regions of the human gene encoding the sodium/iodide symporter, which may account for the lack of expression of the gene in dedifferentiated thyroid cancer cells and/or the lack of iodide uptake in the cell (see, for example, page 8, lines 16-19). For example, the specification teaches that the activation of the gene encoding the sodium/iodide symporter may occur indirectly, since it is possible that demethylation may result in the activation of a second gene encoding a transcription factor that specifically activates the expression of the gene encoding the sodium/iodide symporter (page 9, lines 3-12). However, there appears to be no clear correlation between the presence of the transcription factors, PAX-8 and TTF-1, in a cell line and the expression of the gene encoding the sodium/iodide symporter (page 22, Table 2).

The teaching of the specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims because clearly there is considerable unpredictability, in light of the teachings of the specification, in the art and therefore one skilled in the art cannot predict whether the claimed method can be used effectively without undue experimentation. Because of the fact that there are different mechanisms by which the expression of the gene encoding the sodium/iodide symporter may be regulated, including but not limited to histone acetylation, one of skill in the art certainly cannot predict whether the administration of a demethylating agent will be effective in restoring the expression of the gene. Clearly, there are examples disclosed in the specification of demethylating agents that are incapable of affecting the expression of the gene. Nevertheless, it is apparent that in cases where methylation is

not causative of gene silencing, administration of a demethylating agent cannot possibly be effective. However, the specification provides no exemplification of the claimed method, wherein a deblocking agent other than a demethylating agent is used. On the contrary, it is noted that claim 7 is drawn to a method comprising the use of dimethylsulfoxide, sodium butyrate, and phenylacetate, all of which are *not* commonly referred to as demethylating agents. While 5-azacytidine is generally known to be a demethylating agent, dimethylsulfoxide, sodium butyrate, and phenylacetate are known to be differentiating agents, and further sodium butyrate and phenylacetate are known to be histone-deacetylating agents, which can regulate the expression of genes, albeit by a mechanism that is at least partially independent of DNA-methylation. It is also apparent that there are other mechanisms, apart from a lack of expression of the gene encoding the sodium/iodide symporter, which account for the lack of iodide uptake by a cancer cell. In fact, it is clear from the teachings of the specification that not all dedifferentiated thyroid carcinomas fail to express the sodium/iodide, and yet not all of these carcinomas will respond to radioiodide or ^{99m}Tc-pertechnetate therapy, despite the expression of the gene encoding the sodium/iodide symporter. For example, Matsuda, et al (*Journal of Clinical Endocrinology and Metabolism* **82**: 3966-3971, 1997) teach the presence of a missense mutation in the gene encoding the sodium/iodide symporter of a patient, which results in a defect in iodide uptake by thyroid cells (abstract). In fact, there are a number of examples of studies known in the art that demonstrates the mutational inactivation of the sodium/iodide symporter. Clearly, the claimed method cannot be used by the clinician in cases where the patient's gene encodes an inactive protein; and yet the specification is silent with regard to this issue, providing no guidance in which cells (or patients) should be selected for treatment according to the claimed method. Furthermore, due to the toxicity or lack of specificity of many of the putative unblocking agents, including 5-azacytidine, sodium butyrate, phenylacetate, dimethylsulfoxide, and difluoromethylornithine, one of skill in the art cannot in good conscience practice the claimed invention without first performing extensive and undue experimentation.

Additionally, it is appropriately noted that the specification does not exemplify the use of the method to induce the expression of a gene encoding a therapeutic response element, with the exception of the human gene encoding the sodium/iodide symporter. Clearly, not every agent tested is capable of restoring even the expression of the sodium/iodide symporter or for that matter, of restoring iodide uptake by the dedifferentiated cancer cell. One of skill in the art simply cannot predict whether the claimed method can be used effectively to restore the expression of any gene encoding a therapeutic response element. For example, Kleef, et al (*Cancer Research* **58**: 3769-3772, 1998) teach that, relative to the teachings of the specification, sodium butyrate can have disparate effects upon gene expression. Kleef, et al teach that the expression of the gene encoding the protein Id2 decreased after cells were treated with sodium butyrate (abstract). Finally, it is noted that the specification does not exemplify the use of the claimed method, wherein the expression of a gene encoding an exogenous therapeutic response agent is restored. Also, the specification does not exemplify the use of dimethylsulfoxide in the claimed method. In the absence of exemplification that is commensurate in scope with the claims, in light of the unpredictable nature of the art of cancer therapy, the disclosure is not sufficient to enable one skilled in the art to make and/or use the claimed invention with a reasonable expectation of success without undue experimentation.

11. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for restoring iodide transport to the thyroid typical papillary carcinoma cell line NPA'87, said method comprising a step of administering 5-azacytidine to transcriptionally activate the expression of the previously methylation-silenced gene encoding the human sodium/iodide symporter does not reasonably provide enablement for a method for restoring iodide transport to any dedifferentiated thyroid cancer cell, said method comprising a step of any demethylating agent to transcriptionally activate the expression of any gene encoding a sodium/iodide symporter. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a method for restoring iodide transport to *any* dedifferentiated thyroid cancer cell, said method comprising administering *any* demethylating agent to transcriptionally activate the expression of *any* gene encoding a sodium/iodide symporter. When given the broadest, reasonable interpretation, the claims read on a method of treating a patient diagnosed with dedifferentiated thyroid cancer.

The specification teaches that which is set forth in the 35 USC § 112, first paragraph rejection above. The specification also teaches that only 5-azacytidine was capable of restoring iodide transport to a single dedifferentiated thyroid cancer cell line, namely NPA'87 (page 22, Table 2).

The teachings of the specification cannot be extrapolated to the enablement of the invention, commensurate in scope with the claims, because there is insufficient guidance and exemplification, in view of the unpredictability in the art of cancer therapy and the obvious limitations of the claimed method, and therefore one skilled in the art cannot practice the claimed invention with a reasonable expectation of success without being forced into undue experimentation. The specification teaches that there are numerous mechanisms by which the expression of a gene encoding the sodium/iodide symporter may be repressed or silenced in dedifferentiated thyroid cancer cells (see, for example, page 8, lines 16-19). Therefore, not all patients subjected to treatment with a demethylating agent, according to the claimed method, will be expected to benefit, because clearly not all dedifferentiated thyroid cancer cells will respond to the administration of the agent since a mechanism, other than methylation, may be causative of the gene's lack of expression. While it is appropriately noted that the specification provides no exemplification of the claimed method, wherein a patient is administered a demethylating agent, it is further noted that the specification fails to provide guidance that would serve to instruct the clinician how patients that might be expected to benefit from the treatment can be selected. Moreover, apart from the fact that not all patients will benefit from treatment according the claimed method, it is

apparent that the cost of the treatment may actually outweigh any benefit the treatment may offer. In sharp contrast to the suggestion in the specification that the invention is useful for the treatment of patients diagnosed with thyroid cancer, Thomas, et al (*Carcinogenesis* **13**: 1039-1042, 1992) teach that, at least in rodents, demethylating agents, including 5-azacytidine, causes the production of thyroid tumors (abstract). Obviously, it makes little sense to treat a patient diagnosed with thyroid cancer with an agent that causes the further production of thyroid tumors. Yet, the specification provides no guidance with regard to this issue. Additionally, it is well-known in the art that many of the demethylating or differentiating agents that are claimed to be useful, including 5-azacytidine and sodium butyrate, are actually cytotoxic, effecting the death of normal non-cancerous cells. Evidence of the fact that 5-azacytidine is highly toxic is disclosed in Table 2 of the specification (page 22). As for the other demethylating or differentiating agents of the claimed method, it is noted that the specification actually provides no disclosure that is remotely suggestive of their usefulness. For example, Applicant teaches that both sodium butyrate and phenylacetate are incapable of restoring iodide transport to dedifferentiated thyroid cancer cells (page 22, Table 2). Also, Applicant cited Ormandy, et al (*Endocrinology* **131**: 982-984, 1992) on page 24 of the specification, presumably in support of the concept that sodium butyrate is capable of inducing the expression of a previously silenced gene encoding a therapeutic response element. However, to the contrary, Ormandy, et al teach treatment of cancer cells with sodium butyrate represses the expression of the gene encoding the prolactin receptor (abstact). Certainly in view of the teachings of Ormandy, et al, one skilled in the art would have serious reservations with regard to whether the claimed method can be used effectively to restore iodide transport to dedifferentiated thyroid cancer cells, wherein sodium butyrate is administered to the cells. Furthermore, the specification teaches that none of the agents are capable of restoring iodide transport in anaplastic thyroid cancer (page 7, lines 30-35). In fact, the specification also teaches that with regard to papillary thyroid tumors, methylation of the human gene encoding the sodium/iodide symporter is not associated with the gene's lack of expression (page 15, lines 19-21). Accordingly, it is clear that the claimed method cannot be expected to be

effective, in cases where papillary thyroid cancer cells are to be treated. Finally, Vivaldi, et *al (Journal of Endocrinological Investigation* **23**: 24 (meeting abstract), 2000) teach that the expression of the human gene encoding the sodium/iodide symporter is not correlated with iodide uptake in either primary or metastatic thyroid cancer cells in patients (abstract); therefore, the methylation status of the gene encoding the sodium/iodide symporter apparently has no bearing on the uptake of iodide by dedifferentiated thyroid cancer cells. Thus, the claimed method cannot be expected to be effective, because the re-expression of the previously silenced gene encoding the sodium/iodide symporter in dedifferentiated thyroid cancer cells in patients will not restore iodide transport. Because the claimed method cannot restore iodide transport in thyroid cancer cells in a patient, the invention cannot be used to increase the efficacy of anti-cancer radiotherapy. Obviously, there is considerable unpredictability in the art of cancer therapy since, while a typical papillary cell line (i.e., NPA'87) has been determined to be responsive to the claimed method of treatment, none of the clinically isolated specimens of papillary thyroid carcinoma are expected to be responsive, because the specification teaches that there is no correlation between the lack of expression of the gene encoding the sodium/iodide symporter and the methylation status of the gene. In the absence of exemplification, because the specification teaches nothing to the contrary, clearly the skilled artisan cannot use the invention, commensurate in scope with the claims, with a reasonable expectation of success. Moreover, one skilled in the art cannot predict whether the invention can be used effectively.

In summary, the disclosure is insufficient to meet the requirements of the 35 USC § 112, first paragraph, because the teachings of the specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims and therefore one skilled in the art would be forced into undue experimentation in order to practice the claimed method.

12. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for inducing the expression of a previously silenced gene encoding a therapeutic response element in a cancerous cell, said method comprising a step of administering to the cell an unblocking agent, which causes the re-expression of the gene.

With regard to a gene encoding a therapeutic response element, the specification teaches that the method can be used to activate the re-expression of the gene encoding the human sodium/iodide symporter in selective cell lines. However, when given the broadest, reasonable interpretation, the claims encompass an extraordinarily large genus of genes, which encode a multitude of species of therapeutic response elements. In fact, the specification discloses that "nearly half of all human genes have CpG islands associated with transcriptional start sites" (page 2, lines 15-16), which therefore may be subject to methylation-mediated transcriptional silencing. The number of human genes was recently estimated to be at least 35,000. Adequate description requires more than a mere statement that it is part of the invention. Conception is not achieved until reduction to practice has occurred, regardless of the simplicity of the method. In light of the fact that the claims encompass approximately 17,500, the disclosure of a single species of a gene encoding a therapeutic response element is not sufficient to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time application was filed.

Furthermore, with regard to an unblocking or demethylating agent, the specification teaches that 5-azacytidine is capable of inducing the re-expression of the previously silenced gene encoding the human sodium/iodide symporter in four of seven cell lines tested (page 15, lines 29-31 and page 22, Table 2). However, as the specification discloses, only two of the four cell lines, which responded to treatment with 5-azacytidine, had increased levels of iodide transport following the treatment (page 22, Table 2). Nevertheless, the specification teaches that three demethylating or differentiating agents were tested for the ability to mediate re-expression of the silenced gene encoding the sodium/iodide symporter (page 15, lines 34-35). While no other

agent tested was demonstrated to cause an increase in the level of iodide transport in the previously defective cell, only two agents, namely sodium butyrate and phenylacetate, are shown to be capable of inducing re-expression of the previously silenced gene encoding the sodium/iodide symporter in one cell line. Interestingly, neither sodium butyrate nor phenylacetate had the same effect on any one cell line (page 22, Table 2). Consequently, Applicant discloses only a single species of the vast genus of demethylating agents to which claim 16 is drawn and only three species (which appear to be highly restrictive in activity and dependent upon the cell line treated) of the even larger genus of unblocking agents to which claim 1 is drawn. While non-working embodiments are permissible, certainly the skilled artisan cannot instantly envision the vast genus of unblocking agents that are actually capable of inducing the re-expression of a previously silenced gene encoding a therapeutic response element to which the claims are drawn. The genus of unblocking agents can be subdivided into a number of sub-genuses, which include small organic molecules, peptides, polypeptides, antibodies, nucleic acids, or other materials. Within each of these sub-genuses of putative blocking agents, there are yet other sub-genuses. For example, there is a multitude of activating transcription factors that can be involved in mediating the induced re-expression of the large genus of genes encoding a therapeutic response element. Again, adequate description requires more than a mere statement that it is part of the invention. Conception is not achieved until reduction to practice has occurred, regardless of the simplicity of the method. Therefore, the disclosure of a single species of a gene encoding a therapeutic response element is not sufficient to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time application was filed.

In summary, in view of the above reasoning, it is apparent that the disclosure of a single gene encoding a therapeutic response element, namely the human sodium/iodide symporter, and a single unblocking agent, namely 5-azacytidine, is insufficient to support the generic claims, as provided by the Interim Written Description Guidelines, published in the June 15, 1998 (Federal Register, Volume 63, Number 114, pages

32639-32645). Therefore, the disclosure does not meet the written description provision of 35 USC § 112, first paragraph.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-15 are indefinite because claim 1 recites the phrase "tumor specific" in line 1. While the specification discloses methods for inducing the expression of the gene encoding the sodium/iodide symporter (NIS), the gene is expressed in non-tumor cells and therefore is not tumor-specific. The phrase "tumor specific" is not defined in the specification; however, with regard to gene expression, the phrase "tumor-specific" generally means that the gene is expressed specifically in tumor cells and not in non-tumor cells. In view of the conventional meaning of the phrase, claim 1 appears to be drawn to a subject matter that is not disclosed in the specification as the invention. Claim 16 is also recites the phrase "tumor specific" in line 3 and 4, and is indefinite for this same reason. One of ordinary skill in the art is therefore not reasonably apprised of the metes and bounds of the invention.

Claims 1-15 are also indefinite because claim 1 recites the phrase "blocked from expression" in line 1. While the specification defines "block" as the "inhibition or transcription of a gene" (page 7, lines 8-9). This definition appears to be incongruous, because inhibition of gene expression is generally mediated by blocking either transcription or translation. Therefore, use of the phrase "blocked from expression" renders the claim indefinite. For the same reason, the use of the phrase "unblocking agent" in line 3 also renders claim 1 indefinite. Accordingly, one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention.

Claims 10, 12, and 13 are also indefinite because the claims recite the terms "DFMO", "NIS", and "hNIS", respectively, in parentheses; however it is unclear whether the terms are meant to further limit the claims or are simply parenthetical in nature. If the former, the claims should be amended to delete the parentheses and insert commas to offset the terms. If the latter, the claims should be amended to delete the parenthetical terms.

Claim 10 is also indefinite because the claim recites the phrase "said blocking agent is difluoromethylornithine(DFMO), and adenosyl-1,8-diamino-3-thio-octane". The use of the phrase renders the claim indefinite because it is not clear whether the blocking agent is meant to be either reagent or a combination of both reagents. In any case, the comma between the word "and" in line 2 should be deleted.

Claim 11 is also indefinite because the claim recites the phrase "an untranslated region within the first exon". The use of the phrase renders the claim indefinite because by definition an exon is translated; therefore, there cannot be an untranslated region contained with the first exon of a gene. Thus, one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention.

Claim 16 is indefinite because the claim recites the phrase "a cell" in line 4. The use of the phrase renders the claim indefinite because it cannot be ascertained whether the cell that is defective in iodide transport is one of the cancer cells of line 2 or a different cell. Amending claim 16 to recite the phrase, for example, "in the cancer cells that are defective in iodide transport" in line 4 can obviate this rejection.

Claim 16 is also indefinite because the claim does not recite a positive process step. Amending the claim to recite the phrase, for example, "whereby iodide transport is restored to the dedifferentiated thyroid cancer cell" can obviate this rejection.

Furthermore, claim 16 is also indefinite because the claim recites the phrase "the sodium iodide symporter" in line 5. There is insufficient antecedent basis for this limitation in the claim. Amending the claim to recite, for example, the phrase "a sodium iodide symporter" can obviate this rejection.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1, 2, 4, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Spath, et al (*Molecular and Cellular Biology* **17**: 1913-1922, 1997).

The claims are drawn to a method for expressing a tumor specific therapeutic response element in a cancerous cell in which the expression of the gene encoding the element was blocked, said method comprising administering an agent that re-activates expression of the gene (claim 1), wherein the element is endogenous to the cell (claim 2) or wherein the cell is dedifferentiated and as a result of said administration the gene encoding the element is re-expressed (claim 4) or wherein the expression of the gene encoding the element is activated upon the activation of a transcriptional activator (claim 14).

Spath, et al teach a method for inducing the re-expression of the previously silent HNF1 gene in dedifferentiated liver cancer cells, said method comprising administering to the cell an unblocking agent that re-activates expression of the gene (abstract). Specifically, Spath, et al teach that the unblocking agent, HNF4tag can be administered to the cell by transfection with a gene encoding the agent and that the agent causes the re-expression of the previously silenced genes encoding the therapeutic response factors, HNF1 and a1-AT (page 1915, columns 1). Furthermore, Spath, et al disclose that "HNF4 itself, or its target HNF1, is a positive regulator of HNF4" (abstract), which therefore activates the gene encoding HNF4 causing the gene to be re-expressed. Finally, Spath, et al teach that another unblocking agent, namely azacytidine, can be administered to the cell and that the agent causes the re-expression of a subset of therapeutic response elements (page 1918, column 2).

All the limitation of the claims are met.

17. Claims 1-4, 14, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Avvedimento, et al (*Cell* **58**: 1135-1142, 1989).

The claims are drawn to a method for expressing a tumor specific therapeutic response element in a cancerous cell in which the expression of the gene encoding the element was blocked, said method comprising administering an agent that re-activates expression of the gene (claim 1), wherein the element is endogenous or exogenous to the cell (claims 2 and 3, respectively) or wherein the cell is dedifferentiated and as a result of said administration the gene encoding the element is re-expressed (claim 4) or wherein the expression of the gene encoding the element is activated upon the activation of a transcriptional activator (claim 14) or wherein the cell is derived from a thyroid (claim 15).

Avvedimento, et al teach a method for activating the re-expression of a gene encoding the therapeutic response element, thyroglobulin in cancer cells derived from the thyroid by administering an unblocking agent, namely 5-azacytidine, to the cells (abstract). Avvedimento, et al teach that Kirsten murine sarcoma virus-transformed thyroid cancer cells lose their transformation phenotype (i.e., become dedifferentiated) when grown at a particular temperature; however, the cells still fail to express the gene encoding thyroglobulin (abstract). Upon treatment of the dedifferentiated cells with 5-azacytidine, the cells re-express the exogenous gene, which is fused to a marker gene (page 1136, column 2). Furthermore, Avvedimento, et al disclose that "treatment of the shifted cell with the DNA demethylating agent 5-azaC [5-azacytidine] both reactivated pTg [the promoter of the gene encoding thyroglobulin] and restored TgTF1 activity" (page 1140, column 1). Accordingly, Avvedimento, et al teach that 5-azacytidine treatment also restored the expression of the endogenous gene encoding thyroglobulin (page 1140, column 1). Finally, Avvedimento, et al disclose that "TgTF1 is a trans-acting factor required for pTg transcription and that the block to thryoglobulin expression in Ras-transformed cells is due to inactivation of TgTF1" (page 1140, column 1). Therefore, the activation of TgTF1, a transcriptional activator of the gene encoding thyroglobulin, accounts for the re-activation of the expression of the gene.

All the limitations of the claims are met.

18. Claims 1, 2, 4, 12, 13, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Schmutzler, et al (*Biochemical and Biophysical Research Communications* **240**: 832-838, 1997).

The claims are drawn to a method for expressing a tumor specific therapeutic response element in a cancerous cell in which the expression of the gene encoding the element was blocked, said method comprising administering an agent that re-activates expression of the gene (claim 1), wherein the element is endogenous to the cell (claim 2) or wherein the cell is dedifferentiated and as a result of said administration the gene encoding the element is re-expressed (claim 4) or wherein said element is the human sodium-iodide symporter (claims 12 and 13) or wherein the cell is derived from a thyroid (claim 15).

Schmutzler, et al teach a method for inducing the expression of the previously silenced gene encoding the human sodium/iodide symporter (hNIS), a therapeutic response element, in dedifferentiated thyroid cancer cells by administering retinoic acid to the cells (abstract). The gene encoding hNIS is endogenous to the cancer cell.

All the limitations of the claims are met.

19. Claims 1, 2, 4, 12, 13, 15, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Herle, et al (*Journal of Clinical Endocrinology and Metabolism* **71**: 755-763, 1990), as evidenced by Schmutzler, et al (*Biochemical and Biophysical Research Communications* **240**: 832-838, 1997).

Claims 1, 2, 4, 12, 13, and 15 are drawn to a method for expressing a tumor specific therapeutic response element in a cancerous cell in which the expression of the gene encoding the element was blocked, said method comprising administering an agent that re-activates expression of the gene (claim 1), wherein the element is endogenous to the cell (claim 2) or wherein the cell is dedifferentiated and as a result of said administration the gene encoding the element is re-expressed (claim 4) or wherein said element is the human sodium-iodide symporter (claims 12 and 13) or wherein the

cell is derived from a thyroid (claim 15). Claim 16 is drawn to a method for restoring iodide transport to dedifferentiated thyroid cancer cells comprising a step of administering a demethylating agent to activate the re-expression of the gene encoding a sodium/iodide symporter.

Schmutzler, et al provides evidence of the inherent effects upon dedifferentiated thyroid cancer cells caused by administering an unblocking agent, namely retinoic acid, to the cells.

Van Herle, et al teach a method for restoring the iodide transport to dedifferentiated human thyroid cancer cells, namely follicular carcinoma, said method comprising a step of administering a demethylating agent, namely retinoic acid, which, as evidenced by the teachings of Schmutzler, et al, causes the re-expression of the previously silenced gene encoding the human sodium/iodide symporter.

The method of the prior art comprises the same method steps as claimed in the instant invention, that is, administering an unblocking agent to the same population of cells; thus, the claimed method is anticipated because the method will inherently lead to conferring re-expression of the previously silenced gene encoding the human sodium/iodide symporter in the dedifferentiated thyroid cancer cells. *See Ex parte Novitski* 26 USPQ 1389 (BPAI 1993).

Furthermore, it is well known in the art that treatment of cells with retinoic acid causes differentiation, which is accompanied by the development of DNA-hypomethylation. However, with regard to the limitations in claim 16, retinoic acid is not generally referred to as a demethylating agent, but rather as a differentiating agent. (Similarly, it is noted that the "demethylating agents" of claim 7, namely dimethylsulfoxide, sodium butyrate and phenylacetate, are not generally referred to a demethylating agents, but rather as a differentiating agents.) Nevertheless, retinoic acid appears to have the same properties as the demethylating agent of claim 16, since treatment with retinoic acid causes restoration of iodide transport in dedifferentiated thyroid cancer cells. Therefore, the prior art agent is deemed to be the same as the agent of the instant claim, absent a showing of any differences. The office does not have the facilities for examining and comparing applicant's agent with the agent of the

prior art in order to establish that the agent of the prior art does not possess the same material, structural, and functional characteristics of the claimed agent or would not function identically in the claimed method for restoring iodide transport to dedifferentiated thyroid cancer cells. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed probe and primer are functionally different than those taught by the prior art and to establish patentable differences. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Board of Patent Appeals and Interferences).

20. Claims 1, 2, 5-8, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Swafford, et al (*Molecular and Cellular Biology* **17**: 1366-1374, 1997).

The claims are drawn to a method for expressing a tumor specific therapeutic response element in a cancerous cell in which the expression of the gene encoding the element was blocked, said method comprising administering an unblocking agent that re-activates expression of the gene (claim 1), wherein the element is endogenous to the cell (claim 2), or wherein said gene is methylated on CpG islands in a regulatory region or a coding region (claim 5) wherein the unblocking agent is a demethylating agent (claim 6) wherein the demethylating agent is 5-azacytidine (claim 7) or wherein the demethylating agent is an inhibitor of DNA-methyltransferase activity (claim 8), or wherein said regulatory region is an untranslated region (claim 11).

Swafford, et al teach a method for restoring the expression of a silenced gene encoding a therapeutic response element, namely $p16^{INK4a}$ by administering to a cancer cell an unblocking agent, namely 2'-deoxy-5-azacytidine (abstract). The gene encoding $p16^{INK4a}$ is endogenous to the cancer cell. 2'-Deoxy-5-azacytidine is a well-known inhibitor of DNA-methyltransferase activity. The gene encoding $p16^{INK4a}$ is silenced in the cancer cell because the CpG islands in the gene's regulatory region and/or coding region, including the untranslated region of the first exon, is hypermethylated, which results in transcriptional silencing (see, for example, page 1366, column 2).

All the limitations of the claims are met.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 1, 2, 3, and 5-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swafford, et al (*Molecular and Cellular Biology* **17**: 1366-1374, 1997).

The claims are drawn to a method for expressing a tumor specific therapeutic response element in a cancerous cell in which the expression of the gene encoding the element was blocked, said method comprising administering an unblocking agent that re-activates expression of the gene (claim 1), wherein the element is endogenous or exogenous to the cell (claims 2 and 3, respectively), or wherein said gene is methylated on CpG islands in a regulatory region or a coding region (claim 5) wherein the unblocking agent is a demethylating agent (claim 6) wherein the demethylating agent is 5-azacytidine (claim 7) or wherein the unblocking agent is an inhibitor of DNA-methyltransferase activity (claim 8), or wherein the unblocking agent causes depletion of polyamines (claim 9) wherein the agent is difluoromethylornithine (claim 10), or wherein said regulatory region is an untranslated region (claim 11).

Swafford, et al teach that which is set forth in the 35 USC § 102(b) rejection above. However, Swafford, et al do not expressly disclose that alternatively to administering a demethylating agent (e.g., 2'-deoxy-5-azacytidine), an unblocking agent that mediates an inhibition of *de novo* DNA-methylation of the gene encoding the therapeutic response element by depletion of the reservoir of polyamines can be used to effect re-expression of the previously silenced gene. Furthermore, Swafford, et al do not teach that 5-azacytidine can be used in place of 2'-deoxy-azacytidine.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute α-difluoromethylornithine (DFMO) for the

unblocking agent of Swafford, et al, because it is well known in the art that DFMO causes a state of DNA-hypomethylation and therefore would have the same intrinsic effect that 2'-deoxy-5-azacytidine has on a cancer cell, namely the inhibition of *de novo* methylation of the gene encoding the therapeutic response element, which was previously silenced by methylation. One of ordinary skill in the art would have been motivated at the time of the invention to substitute DMFO for 2'-deoxy-5-azacytidine in order to confirm the results of an analysis in which 5-azacytidine was used to effect re-expression of a previously silenced gene in a dedifferentiated thyroid cancer cell, because it is always desirable to demonstrate that an observed effect is mediated by the suspected mechanism. Because both DMFO and 2'-deoxy-5-azacytdine inhibit *de novo* methylation by different mechanisms, if both reagents cause the same effect upon gene expression, then one may conclude that DNA hypomethylation is responsible for re-expression of the gene.

Similarly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute 5-azacytidine for 2'-deoxy-azacytidine, because the former is also well-known in the art as a demethylating agent that inhibits the activity of DNA-methyltransferases. One would have been motivated to substitute 5-azacytidine for 2'-deoxy-azacytidine, because both reagents have the same intrinsic effect upon the cell and are conventionally used to inhibit DNA-methylation.

Finally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a demethylating agent, namely 5-azacytidine or 2'-deoxy-5-azacytidine, to induce the re-expression of an exogenous gene encoding a therapeutic response element in a cancerous cell, wherein the exogenous gene was silenced by methylation of the CpG islands contained in the regulatory regions of the gene, because it would be desirable to maintain expression of an exogenous gene, otherwise transfecting the exogenous gene into the cell would have had little purpose. One of ordinary skill in the art at the time the invention was made would have been motivated to induce the re-expression of the methylation-silenced exogenous gene, because reactivation of the exogenous gene, which encodes the tumor suppressor $p16^{INK4a}$, can be useful in the reverting the transformed phenotype of the cell.

23. Claims 1, 2, 3-11, 14, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Graff, et al (*Cancer Research* **58**: 2063-2066, 1998).

The claims are drawn to a method for expressing a tumor specific therapeutic response element in a cancerous cell in which the expression of the gene encoding the element was blocked, said method comprising administering an unblocking agent that re-activates expression of the gene (claim 1), wherein the element is endogenous or exogenous to the cell (claims 2 and 3, respectively), or wherein said cancerous cell is dedifferentiated and as a result of said administration the gene encoding the element is re-expressed (claim 4), or wherein said gene is methylated on CpG islands in a regulatory region or a coding region (claim 5) wherein the unblocking agent is a demethylating agent (claim 6) wherein the demethylating agent is 5-azacytidine (claim 7) or wherein the unblocking agent is an inhibitor of DNA-methyltransferase activity (claim 8), or wherein the unblocking agent causes depletion of polyamines (claim 9) wherein the agent is difluoromethylornithine (claim 10), or wherein said regulatory region is an untranslated region (claim 11), or wherein the expression of the gene encoding the element is unblocked by the activation of a transcriptional activator of the gene (claim 14), or wherein the cell is derived from a thyroid (claim 15).

Graff, et al teach that the CpG islands contained in the regulatory elements and coding regions, including the first exon, of the gene encoding the therapeutic response element E-cadherin are densely methylated (page 2063, column 2). Graff, et al teach that E-cadherin is a suppressor of invasion and metastasis in cancer cells (abstract). Graff, et al teach that thyroid carcinoma cells dedifferentiate since the expression of E-cadherin is lost (abstract). Finally, Graff, et al teach that the dense hypermethylation of the CpG islands contained within the regulatory region of the gene encoding E-cadherin in dedifferentiated thyroid cancer cells causes the expression of the gene to be lost (see, for example, page 2064, column 1).

However, Graff, et al do not teach that a method for inducing the re-expression of the previously silenced gene encoding E-cadherin in the dedifferentiated thyroid cancer

cells by administering to the cells a demethylating agent, namely 5-azacytidine or difluoromethylornithine.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to treat the dedifferentiated thyroid cancer cells of Graff, et al with a demethylating agent, namely 5-azacytidine or difluoromethylornithine, to cause the demethylation of the gene encoding the therapeutic response element E-cadherin, because Graff, et al teach that the CpG islands contained within the regulatory elements of the gene encoding E-cadherin in the dedifferentiated thyroid cancer cells are densely methylated, a condition which is commonly known to repress the transcriptional activity of a gene's promoter, and because both 5-azacytidine and difluoromethylornithine are well-recognized demethylating agents that are known to restore the expression of genes that are silenced by hypermethylation in cancerous cells. One of ordinary skill in the art would have been motivated at the time the invention was made to treat the dedifferentiated thyroid cancer cells of Graff, et al with 5-azacytidine to induce the re-expression of the previously silenced gene encoding E-cadherin, because Graff, et al teaches that E-cadherin is a suppressor of invasion and metastasis and therefore the re-expression of the gene encoding E-cadherin can ameliorate the metastatic potential of the cancer cells.

Finally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a demethylating agent, namely 5-azacytidine or difluoromethylornithine, to induce the re-expression of an exogenous gene encoding a therapeutic response element in a dedifferentiated thyroid cancer cell, wherein the exogenous gene was silenced by methylation of the CpG islands contained in the regulatory regions of the gene, because it would be desirable to maintain expression of an exogenous gene, otherwise transfecting the exogenous gene into the cell would have had little purpose. One of ordinary skill in the art at the time the invention was made would have been motivated to induce the re-expression of the methylation-silenced exogenous gene, because reactivation of the exogenous gene, which encodes the tumor suppressor E-cadherin, can be useful in the reverting the transformed phenotype of the cell by blocking its metastatic potential.

Conclusion

24. No claims are allowed.

25. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Grunwald, et al and Simon, et al both teach methods similar to the method of Van Herle, et al, in that the methods comprise a step of administering retinoic acid to a patient to effect an increased level of iodide uptake by the patients' thyroid cancer cells.

Venkataraman, et al teach the extent of success and some of the limitations of using the 5-azacytidine, phenylacetate, or sodium butyrate to restore the expression of the gene encoding the human sodium/iodide symporter and in the case of one cell line, the uptake of iodide.

Behr, et al teaches that in contrast to other thyroid-specific genes, the promoter region of the gene encoding the sodium/iodide symporter contains numerous CpG islands and appears to lack a consensus PAX-8 binding site. Schmitt, et al teach that PAX-8 and TTF-1 play less important roles in regulating the expression of the gene encoding the sodium/iodide symporter than other thyroid-specific genes.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Art Unit 1642

slr
May 7, 2001

DONNA WORTMAN
PRIMARY EXAMINER